or $-(CH_2)_5-$

, said composition being present in a amount sufficient to supply about 0.1 to about 100 mg of compound I per kilogram of body weight of the patient per day; and

b) 5% to 95% of a pharmaceutically acceptable inert carrier material, said composition being formulated in a unit dosage form.

REMARKS

Reconsideration of the claims of record is requested in view of the above amendments and following remarks.

Applicants acknowledge the telephonic restriction requirement of April 18, 1985, wherein the claims of Group I were elected. Claims 1-20 read on Group I.

Claims 21-23, which are directed to a non-elected invention, are withdrawn from consideration and cancelled pursuant to Rule 142(b). Applicants reserve the right to file a divisional application to the cancelled claims.

In the Office Action, the specification was objected under 35 U.S.C. 112, first paragraph for a plurality of reasons to which applicants provide the following responses. Firstly, as

requested, applicants provide a Declaration satisfying the requirements for a deposition of microorganisms under MPEP 608.01(p).

Secondly, applicants submit that the specification is enabling for a "commercially ——produced foodstuff". Establishing a dosage range for formulations of compound I with "foodstuffs" is within the skill of an artisan. More particularly, the daily dosage range of about 0.1 to about 100 mg of compound I per kilogram of body weight indicated at page 13, lines 36-38 of the specification is applicable to foodstuffs such as those described on page 14, lines 9-10 of the specification (e.g. butter, chocolate etc.). Such foodstuffs conveniently contain about 0.1 to 5% by weight of compound I.

Thirdly, according to the Office Action, no enablement is seen for the treatment of obesity in mammals and reduction of triglycerides is not correlated with reduction of fat cells in mammals. Applicants respectfully suggest that the specification is enabling for the treatment of obesity in mammals with compound I.

More particularly, page 5 of the specification sets forth the mechanism of action of compound I. The digestion of

triglycerides received with food is effected in the intestine by pancreas lipase. The pancreas lipase cleaves the primary ester bonds of the triglycerides, whereby free-fatty acids and 2-monoglycerides result. These resulting products then are resorbed and utilized by the body. Compound I does not reduce the number of fat cells. However, in view of the strong inhibition action of compound I on pancreas lipase, the fats (i.e. the triglycerides) are excreted in unchanged form so that the amount of fats absorbed by (and henced contained in) the fat cells is reduced. Thus, compound I is effective in treating obesity in mammals.

At pages 5 and 6, the specification then sets forth experimental evidence demonstrating the inhibition of pancreas lipase by compound I.

Applicants respectfully submit that except for perhaps mere speculation, there is nothing of record to doubt the truth or accuracy of any statement in the specification concerning the activity of applicants' claimed compounds. Mere doubts or lack of information are not sufficient for maintaining a rejection under 35 USC 112. As stated by the Court of Customs and Patent Appeals in the case In re Marzocchi, 169 U.S.P.Q. 367 (CCPA 1971):

> In any event, it is incumbent upon the Patent Office whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statements in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contestant statement. (Emphasis in original) 169 U.S.P.Q. 370.

See also In re Anderson, 176 U.S.P.Q. 331 (CCPA 1973) and In re Armbruster, 185 U.S.P.Q. 152 (CCPA 1975). Since the present record is devoid of any evidence suggesting applicants' specification is not enabling for compound I, the rejection should be withdrawn.

Fourthly, regarding Table I, column 3, page 6 of the specification, the hyphen in the table neither refers to the lack of toxicity or complete toxicity in oral form. The toxicity of tetrahydrolipstatin is the same as that indicated in Table I for lipstatin, that is, greater than 4,000 mg/kg. Should it be requested, applicants would be prepared to insert this number into the table by way of an Amendment.

Fifthly, in the specification, the symbol "l", signifies liter, not "one". Thus, for example, at page 11, line 16, of the specification, the cultivation can be carried out in 10 liter or 200 liter or 1,000 liter fermentors.

Sixthly, regarding the question in the Office Action on salts, applicants note that there are no "heavy metal and

various other metal salts included" in the culture medium, in addition to the salts which are required for the growth of the microorganisms (see page 11, lines 20 and 25) and the salts present in the water utilized for preparing the culture medium. The latter salts which may be present in trace quantities in the water utilized, have no detrimental effects on the fermentation. Based upon the art and the specification, an artisan would be cognizant of acceptable salts.

Seventhly, according the Office Action, no enablement is seen for maximal production and accumulation times of the claimed compounds and the cultivation stage. Applicants submit that the fermentation described in the examples are lab scale processes. This satisfies the requirements of 35 USC 112. There is no requirement for applicants to maximize production on an industrial scale before an application can be filed.

Eigthly, at page 12, line 36 of the specification, applicants have corrected the spelling of "parenterally."

Ninethly, according to the Office Action, the specification is not enabling for "control in prevention of illnesses". To advance prosecution, the specification has been amended at page 2, lines 20-21 to more particularly recite that the invention concern methods for preventing or treating obesity or

hyperlipaemia in an afflicted mammal. Support is found at page 4, lines 16 through 26 of the specification.

Tenthly, regarding the question in the Office Action for Example 1, submerged aerobic conditions may provide better results than the condition described in the incubation of present Example 1. As noted above, there is no obligation to maximize production conditions. The use of such submerged aerobic conditions would be within the skill of an artisan and is contemplated by the present specification.

For the above reasons, applicants request withdrawal of the rejections to the specification under 35 USC 112, first paragraph.

Claims 1-20 are present. Claim 4 has been amended. Claims 21-23 have been cancelled without prejudice to filing a divisional application thereto.

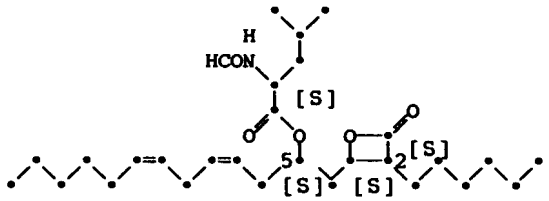
In the Office Action, claims 1-20 were rejected under 35 USC 112, first paragraph for the reasons applicable to the objections to this specification. For the above reasons regarding the specification, applicants submit that the claims of record satisfy the requirements of 35 USC 112, first paragraph.

In the Office Action, claims 4-8 also were rejected under 35 USC 112, first and second paragraphs. According to the Office Action "'No effective amount' of compound is seen in claim 4." To advance the prosecution, applicants have amended claim 4 to recite that the composition is present in a amount sufficient to supply about 0.1 to about 100 milligrams of compound I per kilogram of body weight of the patient per day. Withdrawal of the rejection of claims 4-8 under 35 USC 112, first and second paragraphs is requested.

In the Office Action claims 1-20 were rejected under 35 USC 103 over Umezawa et al.'s U.S. Patents Nos. 4,189,438 (Reference A), 4,202,824 (B) and 4,358,602 (C). Applicants respectfully traverse this rejection.

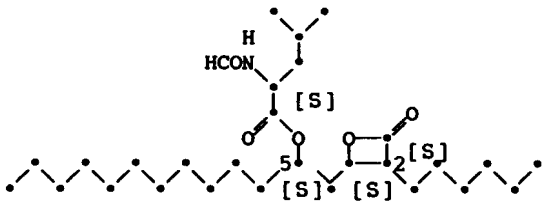
Succinctly, none of the references describes applicants' claimed lipstatin or tetrahydrolipstatin containing an isohexanoyloxy side chain monosubstituted by a formamido group. There is no suggestion in the references to replace the prior art amide function with applicants' isobutanoyl radical which is part of applicants' side chain. To do so requires the use of impermissible hindsight based upon applicants' invention. These and other reasons are set forth in detail hereinbelow.

Applicants' claims are directed to a compound, pharmaceutical composition and methods of use having therein either of the following two compounds having the formulas:



Ia

Lipstatin

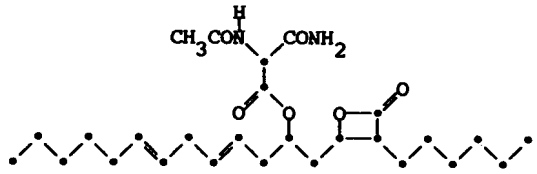


Ib

Tetrahydrolipstatin

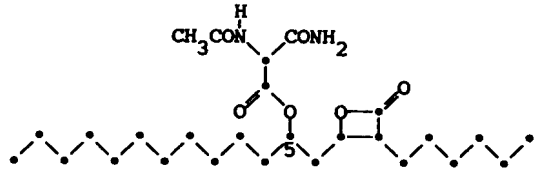
At the 5-position, Applicants' compounds are mandatorily substituted with an isohexanoyloxy side chain monosubstituted by a formamido group. Thus, the compounds contains an isobutanoyl moiety as part of the side chain and a hydrogen atom on the CONH moiety. Additionally, there is a hexyl side chain attached to the two carbon atom of the lactam ring. It is the combination of these three components which give rise to applicants' results in the treatment of obesity and hyperlipaemia.

U.S. Patent No. 4,189,438 describes esterastin of the formula



Esterastin

U.S. Patent No. 4,202,824 describes tetrahydroesterastin of the formula



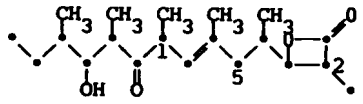
Tetrahydroesterastin

Unlike applicants' compounds, esterastin and tetrahydroesterastin at their 5-position contain a propionyloxy side chain bearing two substituents, i.e. an acetamido and a carbamoyl. Firstly, there is no suggestion to convert the prior art acetamido group to applicants' formamido group.

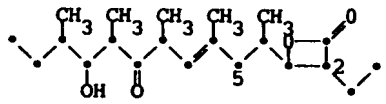
It is noted that the prior art compounds with its methyl group (acetamide) is not sufficient similar to the claimed compound with its hydrogen group (formamide) from the standpoint of structural chemistry to warrant a finding that the claims compounds would be suggested to a chemist from their prior knowledge of the reference compounds. Attention is directed to Ex parte Fonken holding a methyl substituted compound patentable over prior art hydrogen substituted compounds. 133 U.S.P.Q. 691 (Pt. Off. Bd. of App. 1961).

Secondly, there is no suggestion in the references to replace the prior art side chain carbamoyl with applicants' isobutanoyl moiety. There is nothing of record which would motivate a skilled artisan to replace a carbamoyl with an alkyl moiety, let alone applicants' specific branched chain alkyl-isobutanyl. Accordingly, applicants' compounds are not taught by U.S. Patent Nos. 4,189,438 or 4,202,824.

U.S. Patent No. 4,358,602 describes compounds of the formulas:



Ebelactone A



Ebelactone B

Unlike applicants' compounds, ebelactone A and B of U.S. Patent No. 4,358,602 do not have any side chain at the 5-position let alone applicants' isohexanoyloxy side chain monosubstituted by a formamido group. Unlike applicants' compound, the main skeleton of ebelactone A and B contains 5 attached methyl moieties, 1 keto moiety and 1 hydroxy moiety. There is no suggestion in U.S. Patent No. 4,358,602 to eliminate any or all of these moieties. Furthermore, ebelactone A and B contain a methyl or ethyl group respectively attached to the 2 carbon atom of the main skeleton. In contradistinction, applicants' compounds contain a hexyl moiety attached to the 2 carbon atom. Thus, even the main skeleton of prior art ebelactone A and B is structurally dissimilar to that of applicants' claimed compounds.

According to the Office Action, "notable here [U.S. Patent No. 4,358,602] is that absence of the ester linked chain (containing the amide functional group), a modification of the

same portion of which applicant also changes still produces the utility". (Emphasis in the original). Applicants respectfully disagree.

As described above, ebelactones A and B of U.S. Patent No. 4,358,602 differ from applicants' compounds not only in the presence of a side chain but in the main skeleton. To obtain applicants' compounds a skilled artisan would have to modify ebelactones A and B at the 5-position to form an isohexanoyloxy side chain, at the 2-position to form a hexyl group and along the main skeleton to eliminate the methyl, hydroxy and ketone groups. The requirement for making such significant and numerous changes to the ebelactones precludes any comparison of such compounds with the compounds claimed by applicants. Accordingly, applicants' claimed compounds are not taught by U.S. Patent No. 4,358,602.

For the above reasons, withdrawal of the rejection of applicants' claims under 35 USC 103 is solicited.

As requested in the Office Action, applicants have amended the Abstract to recite that the compounds are formed by the cultivation of microorganism Streptomyces toxytricini identified as NRRL 15443.

As requested in the Office Action, applicants have changed the title of the application to 2-HEXYL-3-HYDROXY-HEXADECANOIC ACID LACTONE DERIVATIVES.

The Examiner's attention is directed to the following books which were brought to applicants' attention during prosecution of foreign filings corresponding to the captioned application:

Prescott & Dunn. - "Industrial Microbiology" 4th Ed. AVI Publishing Co. Inc. (1980).

Alba, S., Humphrey, A. & Millis, N. - "Biochemical Engineering". University Tokyo Press. 2nd Ed. (1973).

J. March. - "Advanced Organic Chemistry: Reaction Mechanisms and Structure", McGraw-Hill Book Co. N.Y. (1968).

The Merck Index, Tenth Ed. (1983).

L. S. Goodman & A. Gilman. - "The Pharmacological Basis of Therapeutics" 6th Ed. Macmillan Publishing Company. (1980).

Copies of these books are not included. During foreign prosecution, the books were cited to show the state of the art without more precise indications or comments.

Allowance of the claims of record is solicited.

The Examiner is hereby authorized to call the undersigned attorney of record "collect" on any matter connected with this application. The telephone number is Area Code (201) 235-3656. In the absence of the undersigned attorney of record, the call will be accepted by another attorney empowered in this application.

Respectfully submitted,

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2034P

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Services as First Class Mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231 on July 31, 1985.

George W. Johnston

Attorney for Applicants

Dated July 31, 1985

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application

PAUL HADVARY ET AL. Group 129
Examiner: D. Dinner

Serial No. 621,827, filed June 19, 1984

For: LEUCINE DERIVATIVES

DECLARATION

Hoffmann-La Roche Inc., assignee of the captioned patent application, through its officer, Bernard S. Leon, an Assistant Secretary, does hereby declare that:

(a) during the life of any U.S. patent issuing from the subject application, Hoffmann-La Roche Inc., as assignee, will assure that the microorganism NRRL 15443 which is on deposit at the Northern Regional Research Laboratories, Peoria, Illinois will be permanently available to the public;

(b) access to the above-identified culture will be available during pendency of the patent application to one determined by the Commissioner to be entitled thereto under 37 C.F.R. 1.14 and 35 U.S.C. 122;

(c) all restrictions on the availability to the public of the above-identified culture will be irrevocably removed upon the granting of a U.S. Patent on the subject application which discloses the use of NRRL 15443; and

(d) all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Bernard S. Leon

Dated: July 30, 1985